REMARKS

Claim 57 has been amended. Therefore, claims 57 through 63 are pending in the case. Further examination and reconsideration of pending claims 57-63 are hereby respectfully requested.

DRAWINGS

The Examiner has instructed Applicant that the application is required to furnish drawings under 37 CFR 1.81 for Examiner's review. Applicant is based at the Texas Heart Institute, in the Texas Medical Center, located in Houston, Texas. During several days of intense flooding in Houston, Texas on or about June 2001, archived data including electronic digital photographs upon which the drawings in question were based, was lost or otherwise ruined. Thus, Applicants cannot provide drawings other than those initially provided in the application.

Having said that, Applicant has located the paraffin blocks in which are preserved the same tissues represented in the drawings. Applicant is willing to provide (1) a set of analogous drawings (photographs) based on the identical tissues previously submitted and to provide (2) an affidavit stating how such substitute drawings were derived and that such drawings add no new matter to the application. In the alternative, Applicant is willing to create line drawings based upon the existing photographs and to substitute those line drawings in similar fashion as detailed above.

Applicant requests that the Examiner contact its undersigned representative if the Examiner believes this matter can be resolved in the fashion outlined above. Otherwise,

Applicant requests that the application be examined to the best of the ability of the Examiner based upon the existing drawings, and that this basis of rejection be withdrawn.

SPECIFICATION

Examiner has indicated that numerous pages of the specification have garbled information, specifically pages 3, 4, 5, 11, 12, and 13, and has indicated that correct specifications is required. After consulting with the Examiner as to the best mechanism to correct this matter, Applicant hereby states that it is filing a substitute specification, excluding claims, as allowed by MPEP § 1.125(b) for said correction, in addition to a statement that the substitute specification includes no new matter as required by MPEP § 1.125(b)(1).

CLAIM REJECTIONS – 35 USC § 112

The following is a quotation of the second paragraph of 35 USC 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Examiner rejects Claims 57-63 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In addition, Examiner rejected Claim 57 under 35 USC 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of element, such omission amounting to a gap between the necessary structural connections pursuant to MPEP § 2172.01. Examiner also stated the omitted structural cooperative relationships are: the relationship

between the heating means and the detector. The Examiner also stated the disclosure cites the myocytes may be heated by electrical means delivered via a catheter or the myocytes may be indirectly heated by radio frequency or ultrasound, and the structure of the device is not adequately cited.

Applicant has amended Claim 57 in line with the Examiner's basis for rejection. In particular, Applicant has added the requested cooperative element between the detector and heating element to Claim 57. Support for this limitation can be found beginning in the Specification at page 5 et seq. Thus, it is respectfully requested that this basis for rejection be removed from the case and the claims allowed.

CLAIM REJECTIONS – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 USC 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in pubic use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Examiner rejects Claims 57, 62 and 63 under 35 USC 102(b) as being anticipated by U.S. Patent 5,609,157 to Panescu et al. Panescu discloses a device for treating atrial fibrillation (Col. 3, line 3) that include electrodes for detecting electrical events in myocardial tissue (Col. 5, lines 57-60) and an ablation electrode (Col. 7, lines 22-24). Incorporated by reference U.S. Patent 5,582,609 teaches controlling ablation using temperature feedback providing the capability to

control the temperature to the required range. The detecting electrodes also are capable of monitoring removal of an atrial myocyte by lack of electrical activity.

As will be set forth in more detail below, the § 102 rejections of claims 57, 62, and 63 are respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), MPEP § 2131. The cited art does not disclose all limitations of the currently pending claims, some distinctive limitations of which are set forth in more detail below.

The cited art does not teach means for inducing programmed cell death without the deleterious impact of scarring, blood clotting and myocyte injury caused by ablation devices.

The Examiner ***does not consider the distinction between ablation and apoptosis*** as two different mechanisms of cell death, even though ***these two mechanisms are quite different in their procedures, immediate effects and possible complications.*** Applicant respectfully believes that to fail to consider this distinction is the basis of an error in finding the claimed invention to be anticipated by the cited prior art under the novelty standards.

By way of introduction to the arguments to follow, Applicant would respectfully provide a discussion of the distinctions between the two mechanisms. Ablation is a process whereby either high temperature (e.g. RF ablation) or low temperature (e.g. cryo-ablation) creates immediate physical damage to cells and cellular structures which results in instantaneous cell death. In the case of RF

ablation with high temperatures, this requires temperatures over 50 deg C; and is most commonly practiced with probe temperatures over 80 deg C, in order to decrease procedure times. In RF ablation, the use of temperatures over 60 deg C is strongly preferred as this temperature (or higher) is required to efficiently denature proteins in the cell's structures.

Thus, in RF ablation, the tissue is directly heated by the application of RF energy, and the tissue adjacent to the catheter's therapeutic components will reach temperatures that are warmer than the catheter's "hot" components (and thus warmer than the typical RF-ablation system's feedback temperature sensor located within the catheter). This temperature difference can be significant (up to 15 deg C) if the catheter is positioned so that its temperature sensor is located in (fast) flowing blood, which acts as a coolant to the catheter. Because tissue heated to temperatures over 100 deg C will release (very) problematic gases and because blood-clotting, and such products will build up on hot catheter components at even lower temperatures, most ablations catheter systems are designed to maintain their therapeutically "hot" components between 60 and 85 deg C.

In the case of cryo-ablation with low temperatures, the cells are 'flash-frozen" with the resulting rupture of cellular structures. In cryo-ablation systems, heat is thermally conducted from the tissue to a colder component of the catheter.

No matter what form of ablation energy is used, the nature of ablation is linked to its causing nearly instantaneous cell death and cell lysis. This attribute allows the effects of ablation to be monitored in (near) real-time. In contrast to apoptosis, one downside of all ablation processes is that the healing sequelae create a permanent lesion composed of scar-like tissue. Such lesions frequently cause secondary complications. For example, ablation of the pulmonary veins has been associated

with the onset of pulmonary stenosis and pulmonary venous congestion. In other cases, new arrythmogenic foci may arise in the mixture of normal and scar tissue that forms at the borders of ablation lesions and the surrounding native tissue.

In contrast, apoptosis can be thought of as "cellular suicide" without cell lysis or denaturation of cellular components. Apoptosis occurs naturally as the body's means of continuously revitalizing itself. The lack of cell lysis is the key to differentiating the natural processes following apoptosis versus ablation. In apoptosis, the outcome does not include the formation of a scar-like lesion, which is characteristic with ablation.

More recently, technology has focused on ways to induce specific, selected cells to commit "programmed" cellular suicide over a clinically-valid timeframe (generally hours) as a means of curing or modifying the course of disease. When using heat to induce this much slower "cellular suicide," temperatures of less than 48 deg C are applied over many minutes. Applicant's invention teaches that the narrow therapeutic temperature range for thermally-induced apoptosis is particularly amenable to thermally-conductive delivery. Using RF energy to directly, precisely and mildly heat only the targeted abnormal tissue is problematic. Thus, this is a major difference between Applicant's inventions and the teachings of the prior art patents cited by the examiner relating to RF ablation systems.

As a means of treating atrial fibrillation (the subject of Applicant's invention), inducing apoptosis has many advantages when compared to ablation. Apoptosis is more suited to creating cell death at a single (or at a set of) well defined location(s) without the creation of a scar-like lesion; and thus preventing the initiation of atrial fibrillation in a way that is likely to be even more "permanent"

than ablation-induced scars (with their compromised borders). The clinical potential of apoptosis is less scaring and more normal post-procedure histology. Apoptosis is more than just a substitute method for ablation to create long, linear scar-like lesions that block the atrial fibrillation electrical pathways. This may be particularly advantageous in doing pulmonary vein isolations, by virtue of not causing venous stenosis to develop later with its resulting pulmonary congestion.

Neither prior art patent* cited by the Examiner *teaches the* biological process of *apoptosis, since each such device and method is specifically directed at ablation. Neither the Panescu nor Swanson patents teach the applicability of their inventions for the different clinical needs associated with induced apoptosis. Clearly from the teachings of Panescu and Swanson, neither were aware of the electro-physiologic therapeutic utility of apoptosis, or Panescu and Swanson recognized that their concepts were specific to ablation therapy and not applicable to apoptosis.

Applicant's specification teaches a variety of methods for detecting the potential target sites and for monitoring the induction of apoptosis. These methods include (from section 0013) an "electrical detector," positron emission tomography, differential uptake of specific radio-contrast agents, and thermographic monitoring. In contrast to at least the Swanson prior art reference, Applicant's specification and claims disclose the invention of catheter devices (and methods) for inducing apoptosis to treat atrial fibrillation and other cardiac conditions.

The cited Panescu patent teaches very clearly a general theory of heating tissues, including cardiac tissues, and that general discussion is introduced in a manner making clear that it is directed at cellular destruction not programmed cell death, "Once located, the tissue in the foci can be destroyed or ablated . . . ." Such language clearly teaches away from apoptosis as the therapeutic agent.

Panescu teaches nothing that would anticipate Applicant's inventions of catheter devices (and methods) for inducing apoptosis to treat atrial fibrillation and other cardiac conditions.

In Swanson, (starting with col. 19, line 9), every invention claimed is explicitly linked to at least one independent claim either for "A system for ablating body tissue comprising . . . ," or (in claim 18) for "A method for ablating body tissue comprising the steps . . . ." In Swanson, each independent claim also refers to "at least two electrodes" and each independent claim (except claim 18) calls for "a source of radio frequency energy . . ." (Claim 18 also specifies ". . . to transmit radio frequency energy into tissue . . ."). Clearly, Swanson is teaching the art and disclosing inventions that relate to RF ablation, and the direct RF heating of tissue requiring at least two RF electrodes. In so doing, Swanson teaches away from a device or method of inducing programmed cell death without the deleterious effects of ablation.

Applicant's specification teaches catheter devices (and methods) for inducing apoptosis to treat atrial fibrillation and other cardiac conditions. These methods (see, claim 22) include the administration of TNF-alpha, physical pressure or stretching, or oxidative agents; and/or inducing hypoxia, hypoglycemia, or acidosis. It specifically lacks teachings of methods or devices that will ablate such a tissue and for that reason at a minimum teaches an art that is distinct from that of Swanson.

The present invention clearly discloses catheter devices (and methods) for delivering lower, controlled heat or other gentle, apoptosis-inducing events in order to induce apoptosis (to treat atrial fibrillation and other cardiac conditions) and to avoid ablation. The present invention intentionally is not specific to methods of heating the tissue, but may be practiced with a variety of carefully

controlled techniques including thermally-conducted heating, RF direct heating of the tissue, and perhaps other methods of heating (radiated heat, chemically generated heat, etc.). The key techniques and devices taught by the present invention uniformly involve a lower tissue temperature range and longer durations of heat administration than those taught by Swanson or other ablation-based devices and systems.

Swanson, in particular, specifically teaches away from the present invention in its teachings of causing lesions, and even deep lesions. Swanson for instance teaches techniques to, ". . . form larger and deeper lesions using curvilinear ablating elements." (col. 2, line 6), ". . . without hot spots and gaps forming in the ablated tissue." (col. 2, line 1). This description is consistent with all 18 claims in Swanson. Swanson teaches nothing that would anticipate the Applicant's inventions of catheter devices (and methods) for inducing apoptosis to treat atrial fibrillation and other cardiac conditions.

In order to further the claims to issue, the single independent claim 57 has been amended to further distinguish over the Examiner's basis for rejection. In particular, Applicant has added limitations making clear that the devices and methods of the invention are those specifically intended to avoid the deleterious impact of the prior art ablation devices. Specifically, limitations have been added that distinguish the high temperature ablations of the cited prior art that are designed and teach techniques for necrosis and not for apoptosis. The limitations include eliminating temperature ranges or durations that cause clotting (which leads to stroke), scarring (which can result in pulmonary vein stenosis which when severe has caused pulmonary edema in a significant number of procedures), and myocyte injury (which can weaken the atrium and also can produce new arrhythmogenic regions). Support for this limitation can be found in the

Specification beginning at page 3 et seq. Thus, it is respectfully requested that this basis for rejection be removed from the case and the claims allowed.

For at least the aforementioned reasons, claims 57, 62, and 63 are not anticipated by the cited art. Therefore, claims dependent therefrom are also not anticipated by the cited art for at least the same reasons. Accordingly, removal of the § 102 rejections of claims 57, 62, and 63 is respectfully requested.

CONCLUSION

This response constitutes a complete response to all issues raised in the Office Action mailed December 8, 2003. In view of the remarks traversing rejections presented therein, Applicants assert that pending claims 57-63 are in condition for allowance. If the Examiner has any questions, comments, or suggestions, the undersigned earnestly requests a telephone conference.

Respectfully submitted,

Date: June 8, 2004

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